

**A COMMUNITY-BASED, BIONIC LEG REHABILITATION PROGRAM FOR PATIENTS
WITH CHRONIC STROKE: CLINICAL TRIAL PROTOCOL**

Running Title: Bionic Leg and Rehabilitation in Stroke

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Abstract

Stroke is a major global health problem whereby many survivors have unmet needs concerning mobility during recovery. As such, the use of robotic assisted devices (i.e., a bionic leg) within a community-setting may be an important adjunct to normal physiotherapy in chronic stroke survivors. This study will be a dual-centre, randomized, parallel group clinical trial to investigate the impact of a community based, training program using a bionic leg on biomechanical, cardiovascular and functional outcomes in stroke survivors. Following a baseline assessment which will assess gait, postural sway, vascular health (blood pressure, arterial stiffness) and functional outcomes (6-minute walk), participants will be randomized to a 10-week program group, incorporating either: i) physiotherapy plus community-based bionic leg training program, ii) physiotherapy only, or iii) usual care control. The training program will involve participants engaging in a minimum of 1 hour per day of bionic leg activities at home. Follow up assessment, identical to baseline, will occur after 10-weeks, 3 and 12 months post intervention. Given the practical implications of the study, the clinical significance of using the bionic leg will be assessed for each outcome variable. The potential improvements in gait, balance, vascular health and functional status may have a meaningful impact on patients' quality of life. The integration of robotic devices within home-based rehabilitation programs may prove to be a cost effective, practical and beneficial resource for stroke survivors.

Keywords: robotic assisted, stroke survivors, walking, gait, blood pressure

Introduction

By 2030, stroke burden is expected to double, with increasing survival rates as medical care and treatment techniques improve (1). This leads to an increasing population with diverse stroke-related disabilities, which may include limitations in communication, activities of daily living, co-ordination, balance and mobility (2). It is estimated that following a stroke only 15% of sufferers will gain complete functional recovery for both the upper and lower extremities (3). As such, many stroke survivors continue to have unmet needs, especially concerning mobility (4). Although some individuals with stroke will have received some rehabilitation during the acute and sub-acute phases, rarely does rehabilitation extend beyond one year post-injury due to a lack of resources for long term services (5).

Gait impairment, and therefore a reduction in functional ability, leads to many stroke survivors becoming sedentary. Objective activity monitoring of stroke survivors has showed that >80% of time is spent sedentary, independent of functional ability, and that in the first year post-stroke, there is minimal behavior change (6). With this increased sedentary time, there is a concurrent reduction in fitness and an increased risk of cardiovascular and all-cause mortality and morbidity (7). A reduction in post-stroke fitness could arise from the accumulation of low pre-stroke physical activity and fitness, direct neurological effects of stroke and the effect of post-stroke physical inactivity (8). For many stroke survivors, improving walking ability and mobility is widely regarded to be an important rehabilitation goal (9,10).

Recent advances in medical technology have helped to develop robotic devices to aid gait training in order to restore pre-stroke movement patterns and improve quality of gait for stroke survivors (11). Robotic rehabilitation may help to promote limb function in stroke patients by stimulating neuroplasticity (12) and has the potential to provide intensive, repetitive, and task-specific practice which could enhance functional restitution and improve motor performances (13). Although some robotic devices are large, complex and cumbersome, which necessitates that the therapist be present during use (14), externally wearable commercially available devices that can be independently used during home-based post-stroke rehabilitation are available (15). The integration of robotic therapy into current practice could increase the efficiency and effectiveness of therapists by alleviating the labor-intensive aspects of physical rehabilitation and by enabling novel modes of exercise not currently available. Robotic-assisted gait training has been shown to exhibit significantly greater improvements in gait and balance, as measured by the functional ambulation capacity scale, when compared to regular physiotherapy alone (16). Furthermore, with significant increases in physical activity, step count, and walking capacity observed with the use of lower limb robotic devices (17), such applications may elicit important cardiovascular

benefits for stroke survivors (8). Increases in ambulatory activity has been shown to improve cardiorespiratory fitness and reduce the risk of recurrent cardiovascular events (18).

Research into robotic devices has focused on the implementation within a clinical setting. As patient access to such devices may be constrained by both the accessibility and availability, community-based programs may be efficacious as patients could use such devices more frequently. Despite this, to date, research into robotic devices within a community setting is limited for patients with stroke. Further, studies either have small ($n = 1$) sample sizes (19), or are non-randomized control trials (20). Accordingly, this study will investigate the acute and longer-term effects of using a lower limb robotic device in a community setting on pertinent biomechanical (gait, postural sway), vascular (blood pressure, arterial stiffness) and functional (lower limb strength, 6-minute shuttle walk test) measures in chronic stroke survivors. It is hypothesized that a 10-week community rehabilitation program with a robotic device (bionic leg) will lead to greater changes in the aforementioned outcome measures compared to stroke survivors receiving stand-alone physiotherapy or usual care.

Methods

Research Design

This is a dual-centre, randomized, parallel group clinical trial. Stroke survivors will be identified from a neuro-physiotherapy practice and/or community-based, stroke support groups (Figure 1). All participants will have been diagnosed with stroke by a specialist neurologist/stroke consultant from a UK National Health Service (NHS) Foundation Trust, and will have undertaken normal inpatient and outpatient rehabilitation in accordance with NICE guidelines (21). Participants with a Functional Ambulation Score of 2-5 (22), and who meet the following inclusion criteria are eligible to participate in the study.

Inclusion criteria

- Patients with diagnosis of stroke within 3 months to 5 years of study start date.
- Community patients that are medically stable and are either i) currently receiving physical therapy from a neurophysiotherapy practice, or ii) attending a community-based, stroke support group and do not actively receive physical therapy
- Individuals who are able to stand and step with an aid or with assistance.
- Cognitively aware to undertake rehabilitation exercises, physical therapy and physical activity
- Height: 1.58 to 1.92 m
- Weight: < 159 kg

Exclusion Criteria

- Unresolved deep vein thrombosis, unstable cardiovascular conditions, open wounds, active drug resistant infection, recent fractures of involved limb, peripheral arterial disease, incontinence, severe osteoporosis, non-weight bearing.

Randomization

Web-based randomization procedures will be prepared by an investigator with no clinical involvement in the trial. Participants receiving physical therapy from the neurophysiotherapy practice will be assigned to one of two groups:

- i) a 10-week community-based, bionic leg plus normal physiotherapy program (BL)
- ii) a 10-week normal physiotherapy program (NP)

A third group, recruited from community-based, stroke support groups, will also be assessed in the study:

- iii) Usual care case control group [no physiotherapy program] (CON)

Covariate adaptive randomization is a valid randomization method for clinical research and will be used to ensure balance between BL and NP (23). Covariate adaptive randomization uses the method of minimization by assessing the imbalance of sample size between several covariates. In this study, participants will be sequentially assigned to BL or NP by taking into account the following specific covariates: i) baseline postural sway (only able to stand with an aid vs. able to stand unaided; able to stand ≤ 2 mins vs. able to stand > 2 mins), ii) systolic blood pressure (SBP > 160 vs. < 160 mmHg), iii) age (age > 70 y vs. < 70 y), and iv) time since stroke (< 12 months vs. > 12 months). Allocation will be undertaken by the principle investigator, who will not be involved in assessing patient outcomes. The principal investigator will inform the participant of group allocation. Although participants and a research assistant will be aware of the allocated treatment condition, outcome assessors and data analysts will be kept blinded to the allocation, which will be concealed until the end of the study.

Baseline assessment and outcome measures

Participants will be fasted (> 10 hours), refrain from caffeine consumption for > 12 hours and will not have undertaken moderate-to-strenuous physical activity for > 24 hours prior to the baseline laboratory assessment. Primary and secondary outcome measures will be monitored during the baseline assessment (Figure 1, Table 1). These measures include biomechanical (gait analysis, postural sway),

cardiovascular (central and peripheral blood pressures, arterial stiffness of the carotid artery, blood velocity of the carotid artery) and functional (aerobic fitness, strength) tests. Cardiovascular measures will be completed first, in a supine position, following 20 minutes of supine rest (Figure 2). Biomechanical measures will be recorded whilst standing, and during walking-based movement assessments. Functional measures will be undertaken in both supine and upright seated positions (lower-limb strength tests) and during a physical ambulatory test (aerobic fitness test). On completion of the baseline health assessment participants will also complete a series of questionnaires including the International Physical Activity Questionnaire (IPAQ), Older People's Quality of Life Questionnaire, Functional Ambulation Classification, Dynamic Gait Index, Berg Balance Scale and Trail Making Test (Table 1). Follow up assessments of all primary and secondary assessments will occur at 10-weeks post intervention, 3 and 12 months post.

On completion of the baseline assessment participants will be randomized to either BL or NP, if identified from a neuro-physiotherapy practice, or will be identified from a local stroke support group and will contribute to the usual care control group. Participants will also wear an ActivPal (Glasgow, Scotland) to assess daily physical activity. The monitor will be secured onto the mid rectus femoris for a period of 7 days following the baseline assessment, at 5 weeks mid-intervention, 10-weeks post intervention, 3 and 12 months follow-up.

Bionic leg group (BL)

Participants randomized to the BL group will receive a bionic leg (Alter-G, Fremont, CA, USA) to take home for the duration of the study. Participants will be required to wear the bionic leg for a minimum of 1 hour per day, for a period of 10-weeks. Although recorded, no daily maximum wear-time will be imposed on participants. Settings for the bionic leg will be individualized for each participant, consisting of weight, assistance, resistance, threshold and knee extension angle settings. Participants' progress with the bionic leg will be checked at weeks 2, 4, 6, and 8 by a research assistant. The assistance and threshold settings will be altered in an attempt to elicit progressive overload. Assistance refers to the amount of support the device provides to the participant to help with extension of the lower extremity. This is an approximate percentage of the individual's single-limb bodyweight, whereby a higher value demonstrates a greater contribution from the bionic leg. Threshold refers to the percentage of overall body weight that is necessary through the participant's foot to activate the device's footplate before it will provide assistance. A lower value activates the device with less weight and is therefore more sensitive to small weight shifts making it easier for the participant. Participants will also be provided with a physical activity diary whereby the number of steps, duration of use and activities undertaken while using the bionic leg are recorded daily. During this time, participants will also undertake their regular rehabilitation

therapy at their physiotherapy practice.

Normal physiotherapy group (NP)

Participants will undertake their regular rehabilitation therapy at their local physiotherapy practice. Participants will also be advised to engage in a minimum of 1 hour of physical activity each day for the duration of the 10 week intervention.

Usual care case control group (CON)

Participants will be advised to engage in a minimum of 1 hour of physical activity each day for the duration of the 10-week intervention. These participants will not attend any rehabilitation sessions for the period of the intervention.

Participants in both NP and CON will keep a record of their daily activity recording their total time active, and type of activities undertaken.

Ethical approval and informed consent

The study protocol has received institutional ethical approval. The study has also been registered with the Clinical Trials.gov Protocol Registration and Results System (NCT03104127). Written informed consent will be obtained from all participants prior to the commencement of the study.

Data monitoring body

A research steering committee will meet once every 3 months to discuss data and safety monitoring (i.e., adverse events) and to provide advice on implementation of the research outcomes and outputs. The steering committee will include members of the research team and external stakeholders from the university sector, rehabilitation practice and community.

Sample size

Forty-five participants will be recruited and evenly allocated to each of the three groups (BL, NP or CON) to enable an appropriate sample size to be calculated for a larger trial.

Data analysis

Baseline characteristics of the three study groups will be described by means and standard deviations and percentages as appropriate for the level of measurement and distributions of the data. Baseline characteristics will be compared between groups using a series of one-way analysis of variance

(ANOVA). With the inclusion of the previously identified covariates (baseline postural sway, systolic blood pressure, age, time since stroke), a series of two-way repeated measures analysis of covariance: Condition (BL, NP, CON) by Time (baseline, post-intervention, 3 & 12 month follow-up), will be used to compare all primary and secondary outcome measures. Where statistical differences are observed from the preceding analyses, post-hoc analyses for multiple comparisons will be conducted (Bonferroni adjusted t-tests; Tukeys HSD). An intention-to-treat analysis will be used on all consented participants who are unable to attend the follow-up assessment. Effect sizes will be reported to describe the importance of the relevant findings in practical terms using partial eta squared (η^2), with 0.0099, 0.0588, and 0.1379 representing a small, medium, and large effect (24).

Discussion

With the worldwide burden of stroke expected to continue to rise, there is an ever increasing need to provide efficacious medical and rehabilitation treatment strategies. This is of great importance when considering that only a small proportion of stroke survivors regain complete functional recovery in the years following their stroke diagnosis (3). With stroke survivors often experiencing difficulties with walking, balance and mobility (9,10), lower-limb robotic devices, such as the bionic leg, may provide stroke survivors with the opportunity to improve everyday functional movements. Furthermore, as such devices may elicit an increase in physical activity by increasing the number of steps taken each day, there may be important cardiovascular and quality of life benefits for stroke survivors who engage with such technology during their rehabilitation as it may reduce the risk of future cardio- or cerebrovascular events. With physical therapists often using manual therapeutic approaches to improve upper and lower limb function during face-to-face rehabilitation sessions, the integration of robotic devices within home-based rehabilitation programs may elicit greater improvements in stroke survivors functional health (2,15). Due to the increasing emphasis on moving stroke rehabilitation resources to community-based settings (25), and the overall lack of community-based stroke-rehabilitation research (26,27), there is a need to undertake randomized controlled trials within the community setting to evaluate the importance of using robotic devices.

This study will significantly contribute to our knowledge in using lower-limb robotic devices in a community-based setting for patients with stroke. The potential improvements in gait, walking speed and balance may have a meaningful impact on patients' everyday quality of life. As such, the use of a bionic leg within a community-setting may be an important adjunct to normal physiotherapy in chronic stroke survivors. The study will provide much needed data for stroke patients concerning the biomechanical and physiological effects of training programs incorporating robotic assistive devices. Given the practical implications of the study, the clinical significance of utilising the bionic leg in a 10-week training

program will be assessed for each outcome variable, over both the short- (baseline to post-intervention) and longer-term (3 and 12 month post).

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Table Legend:

Table 1 Study outcomes to be measured at baseline, post-intervention, 3-months, and 12-months follow up

Figure Legends:

Figure 1 Study protocol

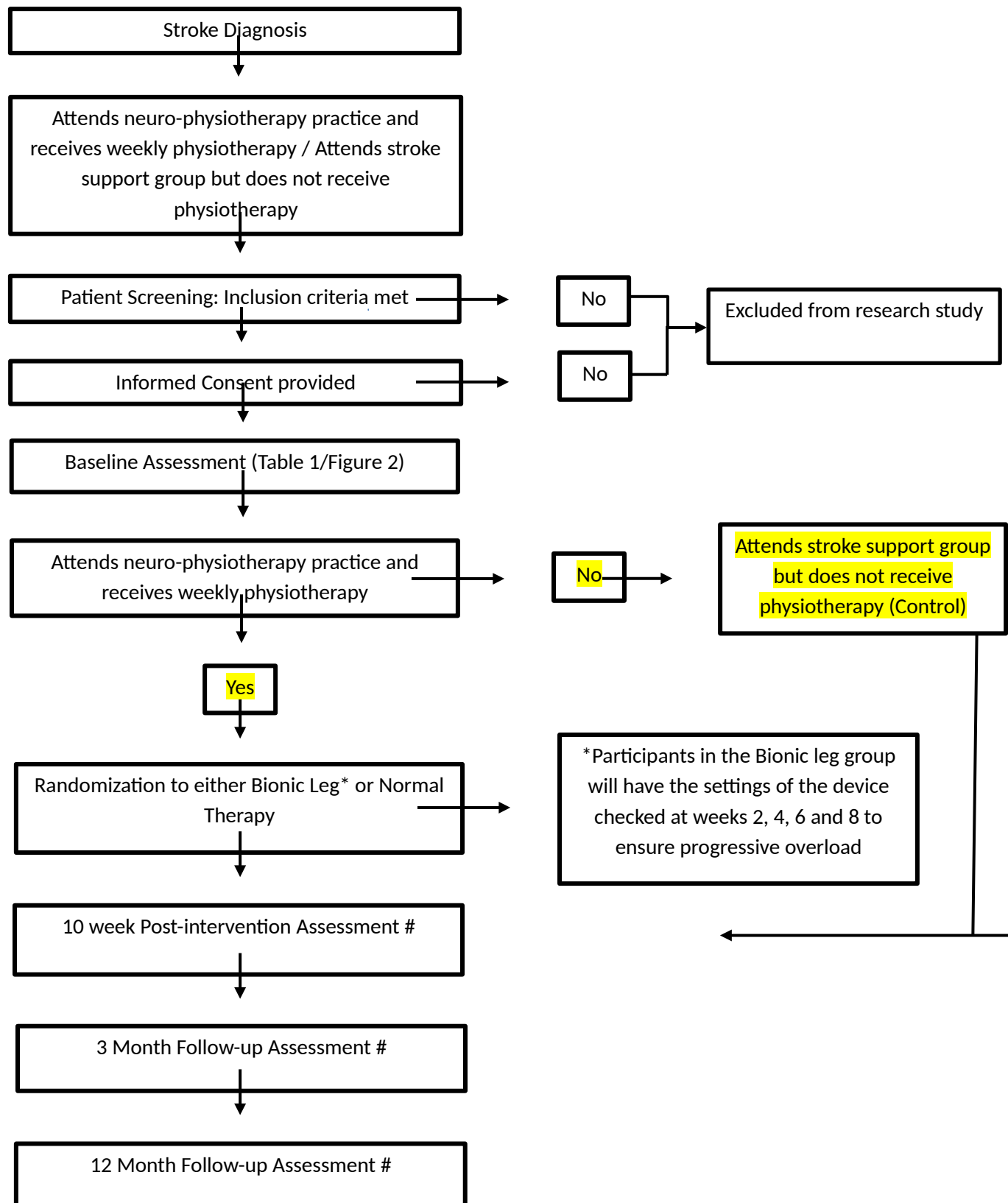
Figure 2 Assessment procedure for baseline, post-intervention, 3 and 12 month follow-up

Table 1 Study outcomes to be measured at baseline, post-intervention, 3-months, and 12-months follow up

Dependent variable	Procedure / measures	Study outcome	Type of measurement
BIOMECHANICAL			
Gait analysis	Eight Qualisys cameras (six Oqus 3+, two Oqus 5+, Goteborg, Sweden) will be used to measure joint angles, rotations, hip obliquity, segment accelerations and velocities. Six Degrees of Freedom 6DoF 27 point marker set will be used and joint centres identified through palpation. The participants will be asked to walk for 6 meters, over a pressure mat (RSscan Footscan, Ipswich, UK), for minimum of three trials in order to obtain walking gait patterns. A BTS G-Walk (Brooklyn, New York) sensor will also be worn by the participants to collect additional spatio-temporal gait parameters (cadence, speed, stride/step length, stance/swing phase duration, single/double support duration and pelvic girdle angles).	Primary	Movement Assessment
Postural sway	Postural sway parameters of maximal anterior-posterior and medio-lateral sway will be calculated on the basis of centre of pressure. Time series will be acquired by means of a pressure mat mounted on top of a Kistler force platform (Kistler, Winterthur, Switzerland). Participants will stand on the pressure mat, unaided if possible, and trials will consist of eyes open shoes on, eyes closed shoes on, eyes open shoes off, eyes closed shoes off. A minimum of three trials will be performed for each condition, each lasting 10s.	Primary	Balance
Ashworth scale	An adapted Modified Ashworth Scale will be used to assess muscle function. This will include the assessment of; Hip flexion, extension, abduction, adduction; Knee flexion, extension; Ankle dorsiflexion, plantar flexion. Each movement will be graded from 0-5.	Secondary	Resistance
PHYSIOLOGICAL			
Health History Questionnaire	Questionnaire to identify family history, personal history and signs and symptoms of cardiovascular disease, and to provide a lifestyle evaluation	Secondary	Rest
Body mass	Body weight, body mass index	Secondary	Rest
Central and peripheral blood pressures	Pulse wave analysis (PWA) will investigate central blood pressures, augmentation index and arterial stiffness following 20 minutes supine rest. Pulse wave velocity (PWV) will also be recorded between the carotid (right and left) and femoral artery, and between the anterior tibial artery (right and left) and femoral artery	Secondary	Rest
Arterial stiffness of carotid artery	Following 20 minutes supine rest, local arterial stiffness of the right and left carotid arteries	Secondary	Rest

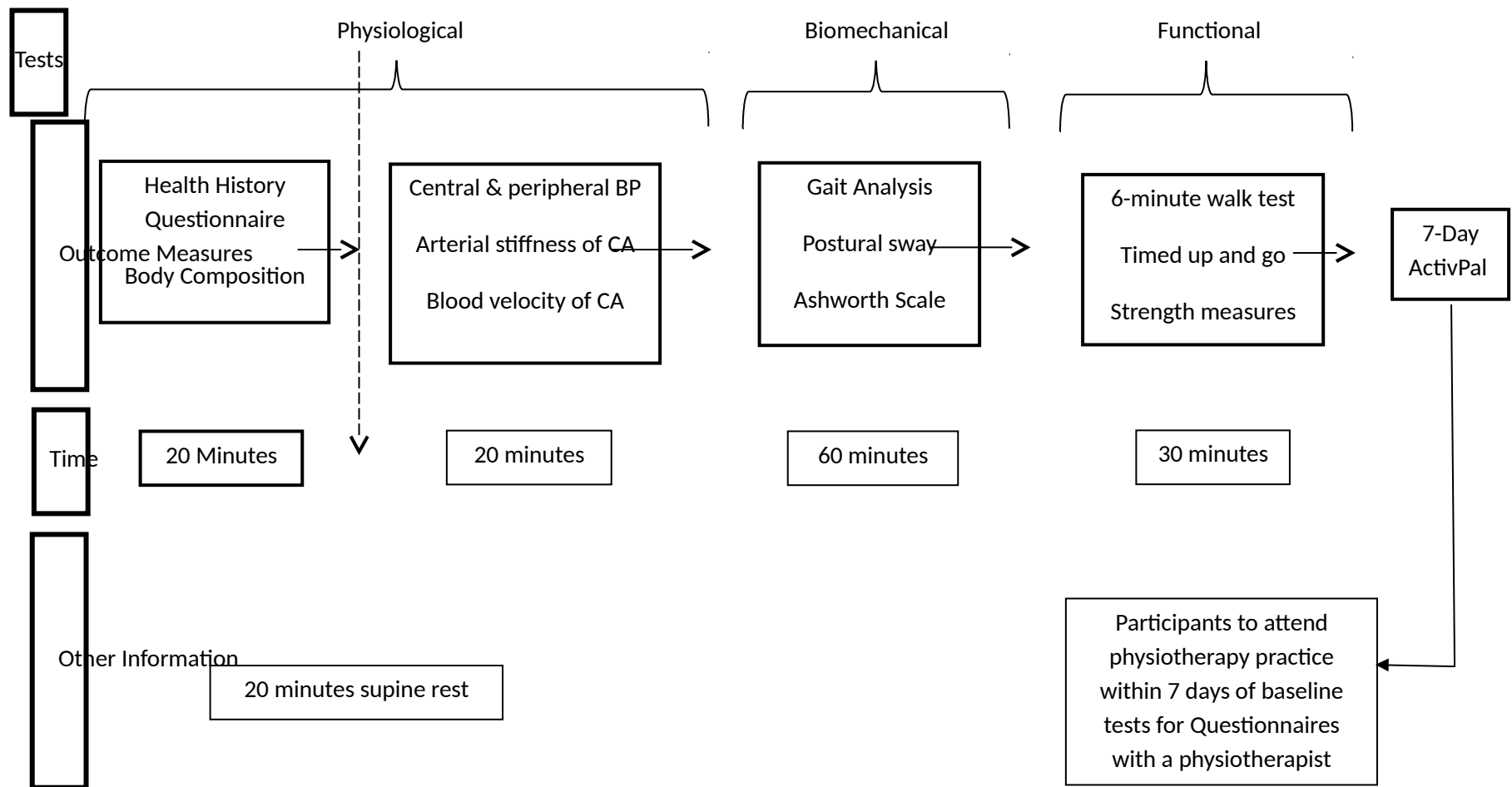
	will be imaged 1-2 cm proximal to the bifurcation using B-mode ultrasound.		
Blood velocity of carotid artery	Doppler ultrasonography will be used to calculate bilaterally volumetric blood flow in the carotid artery. Blood flow will be recorded using a Doppler spectral trace for 1 minute during supine rest.	Secondary	Rest
FUNCTIONAL			
Physical fitness	A 6-minute shuttle walk test will determine total distance walked. Participants' perception of exertion will be measured at 2, 4 and 6 minutes.	Secondary	Physical activity
Timed up-and-go	A BTS G-walk system will be used to collect Timed-Up-and-Go data. From a seated position, participants will stand, walk to a cone 3 m away, walk around the cone, and walk back to the chair sit back down. Participants will complete two familiarisation trials prior to the actual test itself. A minimum of three trials will be performed.	Secondary	Physical activity
Strength	Lower Limb muscle strength will be assessed using a Lafayette hand held dynamometer (Lafayette, USA). Measures will include; Hip abduction, adduction, flexion; Knee flexion, extension; Ankle dorsiflexion, plantar flexion. Participants will be on a massage bed and perform up to three maximal trials for each measure with a minimum of one minutes rest between each measure.	Secondary	Resistance
7-day physical activity	An ActivPal physical activity monitor will be used for 7 days at baseline, 5 weeks into the intervention, and on completion of the 10 week intervention to assess participants' daily physical activity. Measures include; time seated, time standing, ambulation, number of steps, number of sit to stands, and energy expenditure.	Secondary	Physical activity
QUESTIONNAIRES			
Dynamic gait index	8-item test that assesses dynamic balance and gait ability. Scored by rating the participants' performance; walking on a level surface, changing speed while walking, turning the head from side to side and up and down while walking, sudden turns, obstacle negotiation, and stair negotiation. The dynamic gait index has excellent reliability (ICC > 0.94) (28) and validity (r = 0.83) (29).	Secondary	Physiotherapist assessment
Berg Balance	14-item test that assesses static and dynamic balance ability and fall risk in adult populations. Each activity is scored from 0-4, determined by the ability to perform the assessed activity with an overall maximum score of 56. The Berg Balance scale has		

	excellent reliability (ICC > 0.95) and strong correlations with the Fugl-Meyer and Postural Assessment Scale for Stroke patients ($r > 0.90$) (30).
Balance Confidence Scale	16-item self-report measure in which patients rate their balance confidence when performing various ambulatory activities. Rated from 0-100. This scale has excellent test-retest reliability (ICC = 0.85) within the Stroke population (31).
Walking Ability Questionnaire	19-item questionnaire to assess the participant's social limitations resulting from decreased walking ability. Mobility is classified as independent, supervised, assisted, wheelchair or unable for 19 ambulatory activities commonly performed in the home and community.
Functional Ambulation Classification	Assesses functional ambulation in participants undergoing physical therapy. Ranges from non-functional walking to independent walking outside with a scale for 0-5 respectively. The Functional Ambulation Classification has excellent validity with the 6 minute walking test in acute Stroke patients (32).
IPAQ	Collects information on the time spent (number of days and average time per day) spent being physically active (33).
Older Peoples Quality of Life Questionnaire	36-item questionnaire that assesses quality of life. Each question is rated from 0-5 from very bad to very good respectively. The OPQLQ has excellent test-retest reliability (ICC = 0.92) (34)
Trail Making	A neuropsychological test of visual attention and task switching. Consists of two tests, including: i) a test in which the participant is instructed to connect 25 numerical dots in order, and ii) a test in which the participant is instructed to connect 25 numerical and alphabetical dots in order.
Stroop task	Is a measure of prefrontal cortex function (35)



Identical to the baseline assessment

Figure 1 Study protocol



Abbreviations: BP = Blood pressure, CA = Carotid artery

Figure 2 Assessment procedure for baseline, post-intervention, 3 and 12 month follow-up

